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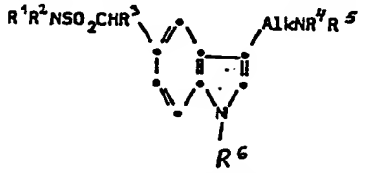
(54) **Indole derivatives.**

(57) Indole derivatives are disclosed of general formula:



wherein R^1 is H, C_{1-6} alkyl or C_{3-6} alkenyl;
R^2 is H, C_{1-3} alkyl, C_{3-6} alkenyl, aryl, ar(C_{1-4})-alkylene, or C_{5-7} cycloalkyl;
R^3 is H or C_{1-3} alkyl;
R^4 and R^5 each represents H, C_{1-3} alkyl or 2-propenyl, or R^4 and R^5 together form an aralkylidene group;
R^6 represents $-CO_2R^7$, COR^7, $-COCO_2R^7$, or $-CONHR^7$, where R^7 represents H, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{2-4} alkenyl, aryl or ar(C_{1-4}) alkylene (with the provisos that (a) R^7 does not represent H or benzyl when R^6 is $-CO_2R^7$ and (b) R^7 does not represent alkenyl when R^6 is $-CONHR^7$);
and Alk represents an alkylene chain containing two or three carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl group, and physiologically acceptable salts and solvates (e.g. hydrates) thereof. The indole derivatives have potent and selective vasoconstrictor activity and are indicated as useful for the treatment of migraine. The indole derivatives may be formulated as pharmaceutical compositions with physiologically acceptable carriers or excipients for administration by any convenient route. Various methods for the preparation of the compounds (1) are disclosed.

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INDOLE DERIVATIVES

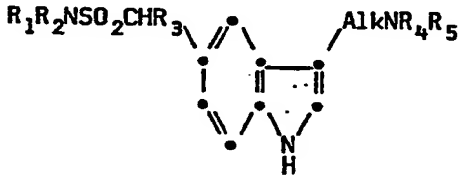
This invention relates to indole derivatives of use in the treatment of migraine, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

The pain of migraine is associated with excessive dilatation of the cranial vasculature and known treatments for migraine include the administration of compounds having vasoconstrictor properties such as ergotamine. However, ergotamine is a non-selective vasoconstrictor which constricts blood vessels throughout the body and has undesirable and potentially dangerous side effects. Migraine may also be treated by administering an analgesic, usually in combination with an antiemetic, but such treatments are of limited value.

There is thus a need for a safe and effective drug for the treatment of migraine, which can be used either prophylactically or to alleviate an established headache, and a compound having a selective vasoconstrictor activity would fulfil such a role.

Furthermore, in conditions such as migraine, where the drug will usually be administered by the patient, it is highly desirable that the drug can be taken orally. It should therefore possess good bioavailability and be effectively absorbed from the gastro-intestinal tract so that prompt relief of symptoms can occur.

A wide variety of indole derivatives have been described as being of use in the treatment of migraine. In our published UK Patent Application No. 2124210A we describe indoles of the general formula



wherein R_1 represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6} alkenyl group; R_2 represents a hydrogen atom or a C_{1-3} alkyl, C_{3-6} alkenyl, aryl, ar(C_{1-4})alkyl or C_{5-7} cycloalkyl group; R_3 represents a hydrogen atom or a C_{1-3} alkyl group; R_4 and R_5, which may be the same or different, each represents a hydrogen atom or a

C_{1-3} alkyl or propenyl group or R_4 and R_5 together form an aralkylidene group; and Alk represents an alkylene chain containing two or three carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl groups, and physiologically acceptable salts and solvates thereof.

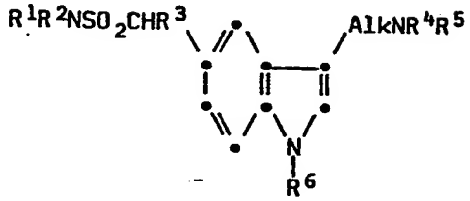
As indicated in UK Patent Application No. 2124210A, compounds of the above formula selectively constrict the carotid arterial bed of the anaesthetised dog and are thus potentially useful for the treatment of migraine.

Preferred compounds described in published UK Patent Application 2124210A include 3-(2-(methylamino)ethyl)-N-methyl-1H-indole-5-methanesulphonamide; 3-(2-aminoethyl)-N,N-dimethyl-1H-indole-5-methanesulphonamide; and 3-(2-aminoethyl)-N-(2-propenyl)-1H-indole-5-methanesulphonamide; and their physiologically acceptable salts and solvates, and a particularly preferred compound described in that specification is 3-(2-aminoethyl)-N-methyl-1H-indole-5-methanesulphonamide, and its physiologically acceptable salts and solvates.

In our published UK Patent Application No. 2162522A we describe a particular compound which falls within the scope of the group of compounds claimed in published UK Patent Application No. 2124210A, but which is not specifically disclosed therein, namely 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide, and its physiologically acceptable salts and solvates. This compound possesses a combination of highly advantageous properties for the treatment of migraine and in this respect has advantages over compounds specifically disclosed in published UK Patent Application 2124210A. Tests in anaesthetised dogs have shown that it potently and selectively constricts the carotid arterial bed following intravenous administration, and also that it is effectively and consistently well absorbed from the gastro-intestinal tract following intraduodenal administration. It's potent and selective vasoconstrictor action has also been demonstrated *in vitro*.

We have now found that certain 1-acyl derivatives of the above indoles exhibit highly potent and selective vasoconstrictor activity following administration to the gastro-intestinal tract.

Thus, the present invention provides an indole of general formula (I):



(I)

wherein R^1 represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6} alkenyl group;

R^2 represents a hydrogen atom, a C_{1-3} alkyl or C_{3-6} alkenyl group, an aryl or ar(C_{1-4})alkylene group, or a C_{5-7} cycloalkyl group;

R^3 represents a hydrogen atom or a C_{1-3} alkyl group;

R^4 and R^5, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl or 2-propenyl group, or R^4 and R^5 together form an aralkylidene group;

R^6 represents a group $-CO_2R^7$, COR^7, $-COCO_2R^7$, or $-CONHR^7$, where R^7 represents a hydrogen atom, a C_{1-4} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-4} alkenyl group, or an aryl or ar(C_{1-4})alkylene group wherein the aryl group is preferably a phenyl group which may be unsubstituted, or substituted by a halogen atom, a C_{1-4} alkyl group, a hydroxy group or a C_{1-4} alkoxy group (with the provisos that (a) R^7 does not represent a hydrogen atom or a benzyl group when R^6 is the group $-CO_2R^7$ and (b) R^7 does not represent an alkenyl group when R^6 is the group $-CONHR^7$); and Alk represents an alkylene chain containing two or three carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl groups, and physiologically acceptable salts and solvates (e.g. hydrates) thereof.

Referring to the general formula (I), an alkyl group may be a straight or branched chain alkyl group preferably containing from 1 to 3 carbon atoms such as a methyl, ethyl, propyl or isopropyl group. An alkenyl group preferably contains 3 or 4 carbon atoms and may be, for example, a propenyl, 2-propenyl or butenyl group. It will be appreciated that when R^1 or R^2 represents a C_{3-6} alkenyl group, the double bond will not be adjacent to the nitrogen atom.

A cycloalkyl group in compounds of formula (I) preferably contains from 5 to 7 carbon atoms and may be, for example, a cyclopentyl, cyclohexyl or cycloheptyl group. An aryl group, either as such or as part of an ar(C_{1-4})alkylene or aralkylidene group, is preferably phenyl. The alkyl moiety in an ar(C_{1-4})alkylene group preferably contains 1 or 2 carbon atoms. An aralkylidene group is preferably an arylmethylidene group and may be, for example, a benzylidene group.

For the substituent R^7, when this is a C_{1-4} alkyl group, it may be for example a methyl, ethyl, propyl, isopropyl or butyl group. When R^7 represents a C_{3-7} cycloalkyl group this may be, for example a cyclopropyl, cyclopentyl or cyclohexyl group.

When R^7 represents a C_{2-4} alkenyl group this may be for example a propenyl, butenyl or isobutenyl group. When R^7 represents a phen(C_{1-4})alkylene group, the alkyl moiety of the group may be a straight chain or branched chain alkyl moiety and is preferably a methyl or ethyl moiety. The alkyl moiety in a C_{1-4} alkoxy group may be a straight or branched chain alkyl moiety and is preferably a methyl or ethyl moiety.

A preferred class of compounds represented by formula (I) is that in which R^1 represents a hydrogen atom or a C_{1-6} alkyl group and R^2 represents a hydrogen atom or a C_{1-3} alkyl, C_{3-6} alkenyl or ar(C_{1-4})alkyl group.

Another preferred class of compounds of formula (I) is that in which R^3 represents a hydrogen atom.

A further preferred class of compounds of formula (I) is that in which R^4 and R^5, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group, for example a methyl or ethyl group. It is preferred that the total number of carbon atoms in R^4 and R^5 does not exceed two.

Another preferred class of compounds of formula (I) is that in which R^6 represents a group $-CO_2R^7$ or $-COR^7$.

A further preferred class of compounds represented by formula (I) is that in which R^7 represents a C_{1-3} alkyl group, for example a methyl or ethyl group, or a phenyl group.

A still further preferred class of compounds falling within the scope of formula (I) is that wherein R^1 represents a methyl group, R^2 and R^3 both represent a hydrogen atom, R^4 and R^5 both represent a methyl group and R^7 represents a methyl, ethyl or phenyl group. Particularly important compounds within this group are those in which R^6 represents the group $-COR^7$ or $-CO_2R^7$, and physiologically acceptable salts and solvates (for example, hydrates) thereof.

Preferred compounds according to the invention include:
Methyl 3-[2-(dimethylamino)ethyl]-5-[[(methylamino)sulphonyl]methyl]-1H-indole-1-carboxylate;
1-Acetyl-3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide;
and physiologically acceptable salts and solvates (for example, hydrates) thereof.

Suitable physiologically acceptable salts of the indoles of general formula (I) include acid addition salts formed with organic or inorganic acids for example hydrochlorides, hydrobromides, sulphates, fumarates, maleates and succinates. Other salts may be useful in the preparation of the compounds of general formula (I) e.g. creatinine sulphate adducts and oxalates.

We have found that compounds of the invention potently and selectively constrict the carotid arterial bed of the anaesthetised dog following intraduodenal administration, whilst having negligible effect on blood pressure. However, the compounds produce no change in carotid vascular resistance following intravenous administration and exhibit no significant vasoconstrictor activity in standard in vitro tests. It is believed that following administration to the gastro-intestinal tract compounds of the invention are converted into the corresponding 1-unsubstituted indoles, i.e. they are prodrugs for the compounds disclosed in published UK Patent Application No. 2124210A and published UK Patent Application No. 2162522A.

Compounds of the invention are therefore useful in treating pain resulting from dilatation of the cranial vasculature, in particular migraine and cluster headache.

Compounds of the invention are suitable for oral, rectal or intranasal administration.

Accordingly the invention provides a pharmaceutical composition adapted for use in medicine which comprises at least one compound of formula (I) or a physiologically acceptable salt or solvate (e.g. hydrate) thereof and which is formulated for oral or rectal administration. Such compositions may be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

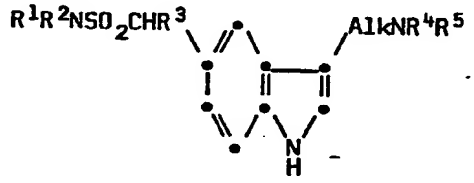
The pharmaceutical compositions for oral administration may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, sucrose, mannitol, maize starch, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. stearic acid, polyethylene glycol, magnesium stearate, talc or silica); disintegrants (e.g. potato starch, sodium starch glycollate or croscarmellose sodium); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, aqueous or oily solutions, syrups, elixirs, emulsions or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives, glucose/sugar syrup, gelatin, aluminium stearate gel, or hydrogenated edible fats); emulsifying agents (e.g. lecithin, acacia or sorbitan mono-oleate); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (eg. methyl or propyl p-hydroxybenzoates or sorbic acid). The liquid preparations may also contain conventional buffers, flavouring, colouring and sweetening agents as appropriate.

For rectal administration the compounds of the invention may be formulated as suppositories or retention enemas e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

A proposed dose of the compounds of the invention for administration to man (about 70kg bodyweight) for the treatment of migraine is 1mg to 1000mg, for example 3mg to 300mg of the active ingredient per unit dose, which could be administered for example 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient, as well as the severity of the condition to be treated.

According to another aspect of the invention, compounds of general formula (I) and their physiologically acceptable salts and solvates (e.g. hydrates) may be prepared by the general methods outlined hereinafter. In the following processes R^1, R^2, R^3, R^4, R^5, R^6 and Alk are as defined for the general formula (I) unless otherwise specified.

According to one general process (A), compounds of general formula (I) may be prepared by acylating a compound of general formula (II):



(II)

or a protected derivative thereof.

Acylating agents corresponding to the group R^6 which may be used in this general process include acid halides (e.g. acid chlorides such as acetyl chloride); alkyl haloformates (e.g. methyl or ethyl chloroformate); mixed or symmetrical anhydrides (e.g. acetic anhydride or benzoic anhydride); carbonates (e.g. ethyl carbonate); and isocyanates (e.g. methyl isocyanate).

The reaction is conveniently effected in the presence of a base, such as an alkali metal hydride, e.g. sodium or potassium hydride; an alkali metal carbonate e.g. sodium or potassium carbonate; an alkali metal alkoxide e.g. potassium t-butoxide; butyllithium; or an organic tertiary amine, e.g. triethylamine, or pyridine.

Suitable solvents which may be employed in the acylation process include amides e.g. dimethylformamide, or dimethylacetamide; ethers, e.g. tetrahydrofuran or dioxan; halogenated hydrocarbons e.g. methylene chloride; nitriles e.g. acetonitrile and esters e.g. ethyl acetate. The reaction may conveniently be effected at a temperature in the range -10 to +150 ^{0}C.

Alternatively the acylation may be effected in a two-phase reaction medium, in the presence of a phase transfer catalyst, such as tetrabutylammonium hydrogen sulphate or tetraethylammonium bromide. Thus for example the acylating agent may be reacted with a compound of formula (II) in an inert organic solvent, (e.g. a halogenated hydrocarbon such as methylene chloride), and an aqueous solution of a base (e.g. 50% sodium hydroxide) containing a phase transfer catalyst.

Compounds of general formula (II) may be prepared for example by the methods described in published UK Patent Application 2124210A.

According to a further general process (B) a compound of formula (I) according to the invention, or a salt or protected derivative thereof may be converted into another compound of the invention using conventional procedures.

For example, a compound of general formula (I) wherein one or more of R^1, R^2, R^4 and R^5 are alkyl groups may be prepared from the corresponding compounds of formula (I) wherein one or more of R^1, R^2, R^4 and R^5 represent hydrogen atoms, by reaction with a suitable alkylating agent such as a compound of formula R^cL where R^c represents the desired R^1, R^2, R^4 or R^5 group and L represents a leaving group such as a halogen atom or a tosylate group, or a sulphate $(R^c)_2SO_4$. Thus, the alkylating agent may be for example an alkyl halide (e.g. methyl or ethyl iodide), alkyl tosylate (e.g. methyl tosylate) or dialkylsulphate (e.g. dimethylsulphate). The alkylation reaction is conveniently carried out in an inert organic solvnt such as an amide (e.g. dimethylformamide), an ether (e.g. tetrahydrofuran) or an aromatic hydrocarbon (e.g. toluene) preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides, such as sodium or potassium hydride, alkali metal amides, such as sodium amide, alkali metal carbonates, such as sodium carbonate; alkali metal alkoxides such as sodium or potassium

methoxide, ethoxide or t-butoxide; and tetrabutylammonium fluoride. When an alkyl halide is employed as the alkylating agent the reaction may also be carried out in the presence of an acid scavenger such as propylene or ethylene oxide. The reaction may be conveniently effected at a temperature of -20^0C to $+100^0C$.

Compounds of formula (I) wherein R^1 represents a C_{3-6} alkenyl group, R^2 represents a C_{3-6} alkenyl, ar(C_{1-4})alkyl or C_{5-7} cycloalkyl group and/or one or both of R^4 and R^5 represents propenyl may be prepared similarly, using an appropriate compound of formula R^cL or $(R^c)_2SO_4$.

According to another general process (C), a compound of general formula (I) according to the invention, or a salt thereof may be prepared by subjecting a protected derivative of general formula (I) or a salt thereof to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the procedure for the preparation of a compound of general formula (I) or a salt thereof it may have been necessary or desirable to protect one or more sensitive groups in the molecule to avoid undesirable side reactions. For example it may be necessary to protect the group NR^4R^5, wherein R^4 and/or R^5 represents hydrogen, with a group easily removable at the end of the reaction sequence.

Such protection may be effected in conventional manner, for example as described in "Protective Groups in Organic Chemistry" Ed. J.F.W. McOmie (Plenum Press 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons 1981). It will be appreciated that the protecting group should be one which can be removed under conditions which do not cleave the acyl group R^6. Thus, for example it may be an aralkyl group such as benzyl which may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal).

As will be appreciated, in either of the general processes (A) or (B) described previously it may be necessary or desirable to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of

general formula (I) or a salt thereof may be carried out subsequent to either of the previously described proceses (A) or (B).

Thus, according to a further aspect of the invention, the following reactions in any appropriate sequence may if necessary and/or desired be carried out subsequent to either of the processes (A) or (B):

(i) removal of any protecting groups; and

(ii) conversion of a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate (e.g. hydrate) thereof.

Where it is desired to isolate a compound of the invention as a physiologically acceptable salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I), with an appropriate acid (e.g. succinic or hydrochloric acid) preferably with an equivalent amount in a suitable solvent (e.g. aqueous ethanol).

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. Thus, for example, the required group at the 5-position may be introduced either before or after cyclisation to form the indole nucleus. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The following Examples illustrate the invention. All temperatures are in ^{0}C.

Example 1

Ethyl 3-[2-(dimethylamino)ethyl]-5-[[(methylamino)sulphonyl]methyl]-1H-indole-1-carboxylate oxalate

A stirred solution of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide (0.5g) in dimethylformamide (10ml) was treated with sodium hydride (0.16g, 80% dispersion in oil) and stirred for 0.5h at room temperature. The solution was cooled to 0^0 and ethyl chloroformate (0.183g, 0.16ml) was added dropwise. The mixture was stirred for 1h at room temperature, quenched with sodium bicarbonate (20ml) and extracted with ethyl acetate (3x30ml). The organic extracts were washed with brine (2x30ml), dried ($MgSO_4$) and concentrated in vacuo to give an oil (0.45g) which was purified by short path chromatography (Merck silica 7747, 20g) eluting with dichloromethane:ethanol:ammonia (100:8:1) to give a solid (0.24g) which was triturated with diethyl ether (20ml) to give a powder (0.143g). The powder was dissolved in hot ethanol (5ml) and heated with a hot solution of oxalic acid (38mg) in ethanol (1ml). The solution was allowed to cool and the crystals that formed were collected and dried at 60^0 in vacuo to give the title compound (0.130g) m.p. 197-198^{0}C

T.l.c. Silica (dichloromethane:ethanol:ammonia = 50:8:1) Rf 0.8 detection u.v., $KMnO_4$

Analysis Found : C,49.8;H,6.4;N,8.8.

$C_{17}H_{25}N_3O_4S.C_2H_2O_4.0.14\ H_2O$ requires: C,49.6;H,6.0;N,9.1%.

H_2O analysis : 0.55% water content ≡ 0.14mol H_2O.

Example 2

Methyl 3-[2-(dimethylamino)ethyl]-5-[[(methylamino)sulphonyl]methyl]-1H-indole-1-carboxylate oxalate

A solution of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulphonamide (1.0g), in dimethylformamide (50ml) was added to sodium hydride (0.2g, 80% dispersion in oil) under a nitrogen atmosphere to give a suspension which was stirred for 2h at room temperature, then cooled to 5^0. Methyl chloroformate (0.32g, 0.26ml), in tetrahydrofuran (5ml) was added dropwise with cooling over 10 min. The reaction

mixture was stirred for a further 1h at 5° and then poured into a mixture of chloroform (50ml) and saturated ammonium chloride (50ml). The chloroform layer was concentrated in vacuo, dissolved in ethyl acetate (50ml) and backwashed with saturated brine (250ml). The organic layer was evaporated in vacuo to give a solid which was purified by chromatography (activated alumina 90, Merck 45g), eluting with dichloromethane:methanol (98:2). The appropriate fractions were combined and evaporated in vacuo to give the 1-acetyl derivative as a solid. The solid (0.445g) was dissolved in hot absolute ethanol and treated with oxalic acid (113mg) in methanol. The crystals (0.43g) that formed were recrystallised from methanol (20ml) and dried in vacuo to give the title compound (0.3g) as a powder m.p. 185-186°. T.l.c. Silica dichloromethane:ethanol:ammonia 50:8:1 Rf 0.5 detection u.v. IPA, $KMnO_4$.

Analysis Found : C,48.6; H,5.7; N,9.3.

$C_{16}H_{23}N_3O_4S.C_2H_2O_4$ requires: C,48.4; H,5.7; N,9.4%.

Example 3

1-Acetyl-3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane-sulphonamide hemioxalate

A solution of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane sulphonamide (1.0g) in dimethylformamide (50ml) was added to sodium hydride (0.2g, 80% dispersion in oil) under a nitrogen atmosphere to give a suspension which was stirred for 2h, then cooled to 5°. Acetyl chloride (0.26g) in tetrahydrofuran (5ml) was added dropwise over 15 min, maintaining the temperature below 5°. The reaction mixture was stirred for a further 1h, and then poured into a mixture of chloroform (50ml) and saturated ammonium chloride (50ml). The chloroform layer was concentrated in vacuo, dissolved in ethyl acetate (50ml) and backwashed with saturated brine (250ml). The organic layer was evaporated in vacuo and the resulting solid was triturated with diethyl ether (250ml) to give a powder (0.44g) which was dissolved in

ethanol (25ml), treated with oxalic acid (119mg) in methanol (25ml) and dried in vacuo to give the title compound (0.15g) as a solid m.p. 208-210°.

T.l.c. Silica dichloromethane:ethanol:ammonia 50:8:1 Rf 0.6

Analysis Found: C,52.4; H,6.3; N,10.4

$C_{16}H_{23}N_3O_3S.0.5C_2H_2O_4.0.3H_2O$ requires : C,52.7; H,6.3; N,10.8.

H_2O Assay indicates 1.28% H_2O = 0.3mol H_2O.

Example 4

1-Benzoyl-3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide oxalate

Benzoic acid anhydride (0.382g) was dissolved in pyridine (5mℓ), cooled to -5° and treated dropwise with a solution of 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulphonamide (0.5g) in pyridine under nitrogen. The solution was heated at reflux for 2h, treated with saturated ammonium chloride and extracted with ethyl acetate. The organic phase was separated and concentrated in vacuo to give an oil which was purified by chromatography (Merck Silica 9385) and eluted with a mixture of dichloromethane: ethanol:ammonia (150:8:1). The appropriate fractions were combined and concentrated in vacuo to give a solid (0.1g) which was dissolved in ethanol (20mℓ) and treated with oxalic acid (31mg, 1 equivalent) in methanol (2mℓ). The crystals that formed were collected and dried at 70° in vacuo for 18h to give the title compound (0.075g) as a solid m.p. 205-208°.

T.l.c. Silica dichloromethane:ethanol:ammonia 150:8:1 Rf 0.3 detection IPA, $KMnO_4$

Assay Found: C,56.2; H,5.6; N,8.2.

$C_{21}H_{25}N_3O_3S.C_2H_2O_4.0.2H_2O$ requires C,56.0; H,5.6; N,8.5%.

H_2O assay contains 0.76 H_2O w/w≡0.2mol H_2O

The following example illustrates a pharmaceutical formulation according to the invention containing 1-acetyl-3-[2-(dimethylamino)-ethyl]-N-methyl-1H-indole-5-methanesulphonamide hemioxalate as the active ingredient. Other compounds of the invention may be formulated in a similar manner.

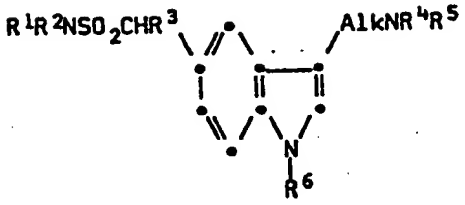
Tablets for Oral Administration

	mg/tablet
Active Ingredient	100
Magnesium stearate BP	1.0
Anhydrous lactose	99

The active ingredient is sieved and blended with the anhydrous lactose and magnesium stearate. The mix is then compressed into tablets using a Manesty F3 tablet machine fitted with 8.0mm concave punches.

CLAIMS

1. A compound of general formula (I):



(I)

wherein R^1 represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6} alkenyl group;
R^2 represents a hydrogen atom, a C_{1-3} alkyl or C_{3-6} alkenyl group, an aryl or ar(C_{1-4})alkylene group, or a C_{5-7} cycloalkyl group;
R^3 represents a hydrogen atom or a C_{1-3} alkyl group;
R^4 and R^5 which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl or 2-propenyl group, or R^4 and R^5 together form an aralkylidene group;
R^6 represents a group $-CO_2R^7$, COR^7, $-COCO_2R^7$, or $-CONHR^7$, where R^7 represents a hydrogen atom, a C_{1-4} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-4} alkenyl group, or an aryl or ar(C_{1-4})alkylene group (with the provisos that (a) R^7 does not represent a hydrogen atom or a benzyl group when R^6 is the group $-CO_2R^7$ and (b) R^7 does not represent an alkenyl group when R^6 is the group $-CONHR^7$); and
Alk represents an alkylene chain containing two or three carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl groups,
and physiologically acceptable salts and solvates thereof.

2. A compound according to claim 1, wherein, in the general formula (I) R^1 represents a hydrogen atom or a C_{1-6} alkyl group and R^2 represents a hydrogen atom or

a C_{1-3} alkyl, C_{3-6} alkenyl or ar(C_{1-4}) alkyl group.

3. A compound according to claim 1 or 2, wherein, in the general formula (I), R^3 represents a hydrogen atom.

4. A compound according to any of claims 1 to 3, wherein, in the general formula (I), R^4 and R^5, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group.

5. A compound according to any of claims 1 to 4, wherein, in the general formula (I), R^6 represents a group $-CO_2R^7$ or $-COR^7$ (where R^7 is as defined in claim 1).

6. A compound according to any of claims 1 to 5, wherein, in the general formula (I), R^7 represents a C_{1-3} alkyl group or a phenyl group.

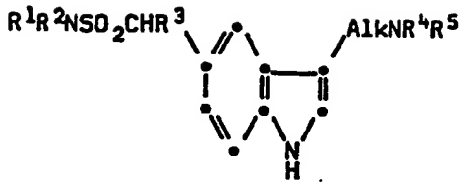
7. A compound according to claim 1, wherein, in the general formula (I), R^1 represents a methyl group, R^2 and R^3 both represent a hydrogen atom, R^4 and R^5 both represent a methyl group and R^7 represents a methyl, ethyl or phenyl group.

8. A compound according to claim 1 selected from methyl 3-[2-(dimethylamino)ethyl]-5-[[(methylamino)-sulphonyl]methyl]-1H-indole-1-carboxylate;
1-acetyl-3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane-sulphonamide.
and physiologically acceptable salts and solvates thereof.

9. A pharmaceutical composition comprising at least one compound of general formula (I) as defined in claim 1, or a physiologically acceptable salt or solvate thereof together with a physiologically acceptable carrier or excipient therefor.

10. A process for the preparation of a compound of general formula (I) as defined in claim 1 which comprises:-

(A) acylating a compound of general formula (II):



(II)

(wherein R^1, R^2, R^3, R^4 and R^5 are as defined in claim 1)

or a protected derivative thereof; or

(B) subjecting a compound of general formula (I) or a salt or protected derivative thereof to an interconversion reaction to form another compound of general formula (I) or a physiologically acceptable salt or protected derivative thereof; or

(C) subjecting a protected derivative of a compound of general formula (I) or a salt thereof to reaction to remove the protecting group or groups to prepare a compound of general formula (I) or a physiologically acceptable salt thereof; and, if necessary or desired, subjecting a compound prepared by step (A) or step (B) to one or two further reactions comprising

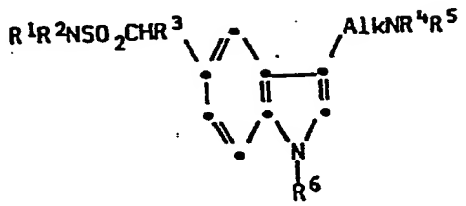
(i) removing any protecting groups; and

(ii) converting a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

Austrian and Spanish

Claims

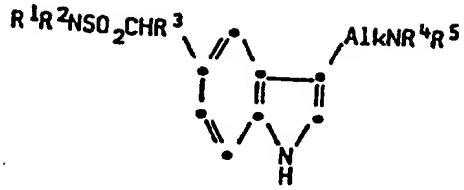
1. A process for the preparation of a compound of general formula (I):



(I)

wherein R^1 represents a hydrogen atom or a C_{1-6} alkyl or C_{3-6} alkenyl group;
R^2 represents a hydrogen atom, a C_{1-3} alkyl or C_{3-6} alkenyl group, an aryl or ar(C_{1-4})alkylene group, or a C_{5-7} cycloalkyl group;
R^3 represents a hydrogen atom or a C_{1-3} alkyl group;
R^4 and R^5 which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl or 2-propenyl group, or R^4 and R^5 together form an aralkylidene group;
R^6 represents a group $-CO_2R^7$, COR^7, $-COCO_2R^7$, or $-CONHR^7$, where R^7 represents a hydrogen atom, a C_{1-4} alkyl group, a C_{3-7} cycloalkyl group, a C_{2-4} alkenyl group, or an aryl or ar(C_{1-4})alkylene group (with the provisos that (a) R^7 does not represent a hydrogen atom or a benzyl group when R^6 is the group $-CO_2R^7$ and (b) R^7 does not represent an alkenyl group when R^6 is the group $-CONHR^7$); and
Alk represents an alkylene chain containing two or three carbon atoms which may be unsubstituted or substituted by not more than two C_{1-3} alkyl groups,
or a physiologically acceptable salt or solvate thereof which comprises:-

(A) acylating a compound of general formula (II):



(II)

(wherein R^1, R^2, R^3, R^4 and R^5 are as defined for formula (I))

or a protected derivative thereof; or

(B) subjecting a compound of general formula (I) or a salt or protected derivative thereof to an interconversion reaction to form another compound of general formula (I) or a physiologically acceptable salt or protected derivative thereof; or

(C) subjecting a protected derivative of a compound of general formula (I) or a salt thereof to reaction to remove the protecting group or groups to prepare a compound of general formula (I) or a physiologically acceptable salt thereof; and, if necessary or desired, subjecting a compound prepared by step (A) or step (B) to one or two further reactions comprising

(i) removing any protecting groups; and

(ii) converting a compound of general formula (I) or a salt thereof into a physiologically acceptable salt or solvate thereof.

2. A process according to claim 1, wherein, in the general formula (I) R^1 represents a hydrogen atom or a C_{1-6} alkyl group and R^2 represents a hydrogen atom or a C_{1-3} alkyl, C_{3-6} alkenyl or ar(C_{1-4}) alkyl group.

3. A process according to claim 1 or 2, wherein, in the general formula (I), R^3 represents a hydrogen atom.

4. A process according to any of claims 1 to 3, wherein, in the general formula (I), R^4 and R^5, which may be the same or different, each represents a hydrogen atom or a C_{1-3} alkyl group.

5. A process according to any of claims 1 to 4, wherein, in the general formula (I), R^6 represents a group $-CO_2R^7$ or $-COR^7$ (where R^7 is as defined in claim 1).

6. A process according to any of claims 1 to 5, wherein, in the general formula (I), R^7 represents a C_{1-3} alkyl group or a phenyl group.

7. A process according to claim 1, wherein, in the general formula (I), R^1 represents a methyl group, R^2 and R^3 both represent a hydrogen atom, R^4 and R^5 both represent a methyl group and R^7 represents a methyl, ethyl or phenyl group.

8. A process according to claim 1, wherein the product is selected from methyl 3-[2-(dimethylamino)-ethyl]-5-[[(methylamino)sulphonyl]methyl]-1H-indole-1-carboxylate;
1-acetyl-3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methane-sulphonamide;
and physiologically acceptable salts and solvates thereof.

9. A process according to any of claims 1 to 8, wherein the acylation step (A) is effected in the presence of a base at a temperature of from -10 to +150°C in the presence of a solvent or in a two-phase reaction medium in the presence of a phase transfer catalyst.

10. A process according to any of claims 1 to 8, wherein in step (B) a compound of general formula (I) wherein one or more of R^1, R^2, R^4 and R^5 are alkyl groups is prepared from a corresponding compound of formula (I) wherein one or more of R^1, R^2, R^4 and R^5 represent hydrogen atoms by reaction with an alkylating agent.

European Patent Office

EUROPEAN SEARCH REPORT

. Application number

EP 87300741.3

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	GB - A - 2 150 932 (GLAXO GROUP LIMITED) * Abstract * --	1,9	C 07 D 209/14 A 61 K 31/40
A	EP - A2/A3 - 0 145 459 (GLAXO GROUP LIMITED) * Abstract * --	1,9	
A	EP - A1 - 0 147 107 (GLAXO GROUP LIMITED) * Abstract * --	1,9	
D,A	GB - A - 2 124 210 (GLAXO GROUP LIMITED) * Abstract * --	1,9	TECHNICAL FIELDS SEARCHED (Int. Cl.4)
P,D A	GB - A - 2 162 522 (GLAXO GROUP LIMITED) * Abstract * ----	1,9	C 07 D 209/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	03-04-1987	HEIN

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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